REMARKS

Interview Summary

Applicants thank Examiner DiNola-Baron for her time and attention in the personal interview held on February 23, 2004. In the interview, Applicants' Representative explained the invention and presented proposed amendments to particularly and distinctly recite the invention. The Examiner agreed to consider the proposed amendments when formally presented in a Reply. The following remarks and amendments reflect the Examiner's comments at the interview.

Status of the Claims

Claims 1, 3-11, 13 and 15-19 are pending in this application. Claims 2, 12 and 14 have been canceled. Claims 15-19 have been added. The claims have been amended to recite a formed product having an inner core and a disintegration layer and optionally having an enteric coating. The claims have also been amended to recite that the formed product is disintegrated in the large intestine. No new matter has been added by the above new claims or claim amendments.

Rejections under 35 USC 103(a)

The Examiner rejects claims 1-14 as obvious over Watanabe et al. USP 6,368,629 (Watanabe '629) in view of EP 0284039 (EP '039). Applicants traverse the rejection and respectfully request the withdrawal thereof.

The present invention is directed to a formed product for releasing an active ingredient in a large intestine part of a lower gastrointestinal tract, comprising: (1) an inner core comprising an active ingredient <c> to be delivered to the large intestine; (2) a disintegration layer surrounding said inner core comprising particles comprising a compound <A> having a molecular weight of 1,000 or less and having a disulfide bond and a polymer <B> having a molecular weight of above 1,000 which forms a matrix in which said particles are dispersed and having a property of being decomposed by enterobacteria, and/or a property of being softened, swelled or dissolved due to a pH in the range of from about 6.8 to about to a lower pH present in the large intestine, wherein the disintegration layer is stable in a small intestine at a pH of about 6.8, but when in the large intestine, the particles of compound <A> are dissolved forming microfine holes in the matrix of polymer <B> for liquid of the large intestine contents to enter the matrix; and (3) optionally an enteric coating surrounding said disintegration layer.

Watanabe '629 is directed to a system for releasing a drug in the colon of the gastrointestinal tract. The drug is coated with an organic-acid-soluble macromolecular substance and a saccharide, which rapidly generates an organic acid when in contact with enteric bacteria in the lower gastrointestinal tract and releases the drug specifically in the colon of the gastrointestinal tract.

Watanabe '629 fails to disclose or suggest a product that has a disintegration matrix layer that is not disintegrated until the disulfide bonds of compound A are broken to create microholes so that the intestinal contents are then permitted to pass into the matrix of the disintegration layer of polymer B only in the large intestines.

The invention in Watanabe '629 is a CODES system. The present invention is not a CODES system. Please see a comparison of a CODES system to the present invention in the attached diagram. The CODES system is characterized by the dissolution of the film due to generated organic acid. However, in the present invention the compound <A> decomposes forming microholes and then the matrix decomposes. Watanabe fails to disclose this type of system.

Watanabe '629 also differs from the present invention in structure. The composition in Watanabe '629 comprises a drug (b) coated with a polymer (a), which is to be dissolved by an organic acid, and a saccharide (c), which rapidly generates the organic

acid by the enterobacteria in the lower GI tract. See, column 4, lines 46-54. Note that the figures in Watanabe (and in the diagram provided herein) show that the polymer (a) and the saccharide (c) are separated in the layer.

Saccharides (c), which can be used with the polymer (a) in the Watanabe '629 invention, are lactulose, reaffinose, cellobiose, stachyose and fructooligosaccharides. These saccharides have high solubility, meaning they are not decomposed by digestive enzymes in the GI tract and are not directly absorbed from the GI tract. The amount of water required to dissolve a 1 gram portion of saccharide is less than 5 ml. Thus, saccharides having a water solubility of higher than 20 weight (w)/volume (v) % are preferred in Watanabe '629. See, column 7, lines 26-46. The saccharides must have this high solubility so that the enterobacteria generate organic acid for dissolving the polymer (a) at the appropriate time.

On the other hand, the phenomena of the disulfide bonds breaking in the compound <A> is the essence of the present invention. Thus, compound <A> must have a molecular weight of 1,000 or less and have disulfide bonds. The enterobacteria cleave the disulfide bonds forming microholes in the matrix of the disintegration layer.

The compound <A> of the present invention has a lower molecular weight. Watanabe '629 fails to suggest a lower molecular weight polymer (a) because the saccharide (c) must be highly

soluble and if that were the case, the composition would decompose early in the GI tract and defeat the purpose of the composition to deliver the drug to the lower GI tract.

The preferred embodiment of the present invention is where compound <A> is cystine. Cystine is hardly soluble in water. Whereas, saccharide (c) in Watanabe '629 is highly soluble in water. The specific solubility of cystine is 0.112 g/L at 25°C and not less than 9000 mL of water is actually necessary to dissolve 1 g of cystine. See the Merck Index attached hereto. Therefore, cystine is at least 1800 times less soluble in water than the saccharide (c) in Watanabe '629. As such, the compound <A> of the present invention is quite different from the saccharide (c) of Watanabe.

Furthermore, when the disulfide bonds in the cystine break from the enterobacteria generating thiol functional groups the molecular acidity is slightly higher. For example, the thiol group of cystine has a proton dissociation constant of 8.33 pKa and this value is significantly lower in terms of the substantial acidity than the organic acid generated by the action of enterobacteria in the Watanabe system. Please note that carboxylic acids, such as acetic acid, propionic acid, and lactic acid have proton dissociation constants of 4.74 pKa, 4.87 pKa and 3.86 pKa respectively. See the Merck Index.

Clearly, the Watanabe composition is different from the product of the present invention in structure and in function.

The Examiner relies on EP '039 for disclosing a composition that contains cystine. Applicants submit that EP '039 discloses a slow-release pharmaceutical composition which comprises at least one kind of molecule selected from a group of adenine, cystine and tyrosine. The Examiner suggests substituting the polymer (a) with the cystine of EP '039.

However, Applicants submit that the cystine of EP '039 is not a polymer and does not have the function of water permeability control. The cystine in EP '039 is a so-called low molecular compound with resistance to water solubility. The low molecular compound in EP '039 is useful for slowly releasing the active ingredient. See page 2, lines 46-51 of EP '039, which describes that "and (5) pharmaceuticals with a coating of water insoluble high molecular weight substances are unable to release the active substance at a predetermined time after their administration; water-soluble high molecular weight substances will immediately swell by an infinite degree and are unable to inhibit the drug release for a prolonged period; enteric high molecular weight substances are unable to perform, time-dependent and not pH dependent, control of the drug release."

Also, the cystine in EP '039 is not used in a site specific manner as in the present invention. EP '039 does not disclose

using cystine as a component in the coating layer. EP '039 uses cystine as a sustained release agent, but does not disclose or suggest the use of the cystine for permitting the composition to reach the large intestine of the GI tract.

From the foregoing, it is clear that the water permeable release controlling material is distinct from the polymer (a) in Watanabe. As such, Applicants submit that there is no motivation to combine Watanabe and EP '039 to arrive at the present invention because Watanabe requires a highly soluble saccharide and a high molecular weight polymer (a). Yet, EP '039 discloses cystine as a low molecular compound that is not very soluble. Further, cystine is not a polymer and does not have the function of water permeable release control.

As such, Applicants submit that no prima facie case of obviousness has been established with respect to combining Watanabe and EP '039 to arrive at the present invention. Particularly, Watanabe is a completely different drug delivery system from the present invention. Watanabe is a CODES system that has lactulose that generates organic acid when reacted with the enterobacteria. On the other hand, the present invention generates microholes in the disintegration layer when the enterobacteria cause the disulfide bonds to break in the compound <A>. EP '039 does not compensate for these shortcomings in Watanabe. Moreover, there is no motivation to use the cystine in EP '039 with the composition of

Watanabe because the cystine in EP '039 is a low molecular compound that is not very soluble and Watanabe calls for a highly soluble saccharide. Thus, Applicants respectfully request that this rejection be withdrawn.

The Examiner also rejects claims 1-14 as obvious over USP 6,004,583 to Plate et al. Applicants traverse the rejection and respectfully request the withdrawal thereof.

Plate '583 discloses a therapeutic-containing composition adapted for oral administration, which comprises a water insoluble but water swellable polymer chemically modified with a chemical agent, which reduces the degradation or deactivation of the therapeutics. Dimethylaminoalkyl methacrylate or chitosan are discloses as examples of these polymers.

Applicants submit that Plate '583 fails to disclose each and every element of the present invention. Plate '583 fails to disclose a compound <A> that has disulfide bonds that will be broken by the enterobacteria in the lower GI tract. Plate '583 discloses that thiol groups of cystine from an inhibitor protein are chemically bound to a polymer. With coupling thiol groups of cystine from an inhibitor protein to a polymer, such as chitosan, the thiol groups are consumed by the reaction by the crosslinking agent. Thus, no disulfide bonds are formed in the modified polymer. As such, there are no disulfide bonds to break

that would create microholes in the matrix disintegration layer as in the present invention.

Plate '583 fails to disclose the layered product of the present invention. Moreover, the cystine in Plate would not break to create holes because there are not disulfide bonds in the modified polymer. Plate '583 also fails to disclose the site specific use of the cystine for creating the microholes by the decomposition of compound <A>.

For the foregoing reasons, Applicants submit that no prima facie case of obviousness has been established because Plate '583 fails to disclose or suggest all the elements of the present invention, particularly the layered system having cystine that create microholes in the disintegration layer.

Conclusion

As Applicants have addressed and overcome all rejections in the Office Action, Applicants respectfully request that the rejections be withdrawn and that the claims be allowed.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kecia J. Reynolds (Reg. No. 47,021) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Gerald M. Murphy, Jr., #28,977

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/KJR/jao
1110-0305P

(Rev. 02/12/2004)